Remarks/Arguments

Claims 39-46 and 49-51 are pending in this application and are rejected on various grounds. The rejections to these claims are respectfully traversed.

Priority

The Examiner states that Applicants are only entitled to the 2/22/00 priority of application PCT/US00/04414 since a conclusion of utility was not reached based on the stimulatory activity demonstrated in the MLR assay. As discussed below, Applicants maintain that the data generated in the MLR assay (Example 74), first disclosed in U. S. Application Serial No. 60/100,858 filed September 17, 1998, establish patentable utility for the invention claimed in this application, therefore the effective filing date of the present application is September 17, 1998.

Claim Rejections – 35 USC § 112

Claims 39-43, 50-51 were rejected under 35 USC § 112, first paragraph, for alleged lack of enablement at the time the application was filed. Applicants respectfully traverse these rejections.

The Examiner acknowledges that MLR is a well-established assay that is useful to assess the immune response of an individual to allogens. However, the Examiner asserts that there is no indication in the art that any *in vitro* immune assay predicts or correlates with immunostimulation and that the MLR assay does not lend utility/use to the instant polypeptide. The Examiner adds that, if one of ordinary skill in the art concluded that the (MLR) assay was not predictive or correlative of immunosuppression, they would also most likely conclude that the assay is not predictive of immunostimulation either. For the reasons outlined below, Applicants respectfully disagree.

Utility Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: **"If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."**

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the Applicant's assertions." (M.P.E.P. 2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

To overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.**

Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Further, the legal standard with respect to *in vitro* or animal model data providing pharmacological activity has been commented on in *Cross v. Iizuka*, 753 F.2nd 1040, 1051, 224 USPQ 739, 747-48 (Fed. Cir. 1985):

> "We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vitro* utility."

Furthermore, M.P.E.P. 2107.03 (III) states that:

> "If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process."

Thus, the legal standard accepts that *in vitro* or animal model data is acceptable utility as long as the data is "reasonably correlated" to the pharmacological utility described.

Arguments

A *prima facie* case of lack of utility has not been established

Previously, the Examiner had quoted exemplary references like Kahan *et al.*, Picotti *et al.* and Campo *et al.* to show that "no *in vitro* immune assay predicts *in vivo* immunosuppressive efficacy." All three references study allograft rejections and immunosuppression of graft rejection using test compounds studied *in vitro*.

However, the Examiner has failed to point out several instances quoted within these references wherein the authors stated that MLR is an important method with a good predictive value. For example, Campo *et al.* teach that "the human mixed lymphocyte culture (MLC) is an important method to test donor-recipient compatibility in bone marrow transplantation. It could

be shown that cytokine release, especially IFN-γ, **has a very good predictive value with regard to the transplantation outcome**, as cytokines play a major role in the generation of an alloreactive immune response and for the induction of graft rejection ***in vivo***.....Landolfo *et al.* inhibited T-cell reactivity by the addition of anti-IFN-γ **both *in vitro* and *in vivo***". (Emphasis added) see page 18, discussion paragraph). Further, Picotti's teachings showed that the IL-12Rβ1 subunit was critical for IL-12 driven enhanced alloimmune response ***in vitro* and *in vivo*** (see abstract). Thus, while there are instances of unpredictability using the MLR assay, there are many studies showing predictable results, including studies from Picotti, Landolfo and the IFN-γ study.

The Utility Guidelines clearly state that "Absolute predictability is not a requirement." Accordingly, one of ordinary skill in the art would not necessarily conclude that the MLR assay is not a predictive or correlative assay. On the other hand, as discussed below, one of ordinary skill in the art would not doubt the truth regarding "immune stimulation" as a utility for PRO217, especially since Picotti's teachings on IL-12 in fact support the Applicants' position. Thus, a *prima facie* case of lack of utility has not been established based on Picotti, Campo and/or Kahan.

PRO217 has utility

Without acquiescing to the propriety of this rejection, solely in the interest of expediting prosecution in this case, Applicants submit a declaration and supportive references from the art to support the immunostimulant activity of PRO217.

Applicants submit a declaration by Sherman Fong, Ph.D. of Genentech, Inc., an expert in the field of Immunology and co-inventor of the present application, to show that there are specific immune stimulant utilities for compounds identified by an MLR assay. The Declaration explains how the MLR reaction was performed in the instant application using peripheral blood mononuclear cells (PBMCs), which contain responder T-cells, and allogenic, pre-treated (irradiated) PBMCs, which predominantly contained dendritic cells. As Dr. Fong emphasizes, immunostimulants are important and are very desirable in the treatment of cancer and in enhancing the effectiveness of previously identified treatments for cancer. Supportive evidence also comes from teachings in the art like Steinman *et al.* (Exhibit B) who states that "...**medicine needs therapies that enhance immunity or resistance to infections and tumors**. (page 1,

column 1, line 7; emphasis added)". Further teachings like Peterson *et al.* (Exhibit D) show that, recently, the immune stimulant IL-12, was successfully used in a cancer vaccine trial to treat melanoma. In fact, Picotti's teachings (quoted by the Examiner) similarly showed that IL-12 enhanced ***in vitro* and *in vivo*** alloimmune response (see abstract). Further, as Dr. Fong explains regarding the IL-12 melanoma trial:

> "Due to the immune stimulatory effect of IL-12, **the treatment provided superior results** in comparison to earlier work, where the patients' own dendritic cells were prepared from peripheral blood mononuclear cells (PBMCs) treated with antigens, then cultured *in vitro* and returned to the patient to stimulate anti-cancer response" (Emphasis added).

Further, Dr. Fong's declaration clearly states that:

> "A PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity of at least 180% of the control is expected to have the type of activity exhibited by IL-12 and would find practical utility as an immune stimulant".

Accordingly, the positive results obtained in this assay clearly establish the immunostimulant utility for the polypeptides claimed in the present application, and the specification, in turn, enables one skilled in the art to use the compounds for the asserted purpose.

By the foregoing arguments and supportive evidence, Applicants have established that the MLR reaction is a generally recognized assay to assess the immunostimulatory activity. Thus, besides the previously asserted immunostimulatory uses of PRO 217, for example, in the treatment of viral infections like HIV or Epstein Barr viral infections, Applicants assert other utilities in the treatment of cancers like melanoma. Further, since the legal standard accepts *in vitro* as acceptable utility and the data is "reasonably correlated" to the pharmacological utility based on the discussions above, a valid case for utility has been made and would be considered credible by a person of ordinary skill in the art. For the same reason, one skilled in the art at the priority date of the present application would have reasonably accepted this utility.

In view of the foregoing arguments and submitted evidence, the Examiner is respectfully requested to reconsider and withdraw the present rejections.

Claim Rejections - 35 USC § 102

1. Claims 39-43 and 44-46, 49 were rejected under 102 (a) as allegedly being anticipated by Hsieh *et al.* (Nature 398: 431-36, 1999) which discloses a polypeptide with 99.7% sequence identity to SEQ ID NO: 4 of the present application.

Once again, in view of the discussions above, the "stimulation of proliferation of T-lymphocytes assay" provides patentable utility and has a priority date of September 17, 1998. The effective reference date of Hsieh is 1999 which is after the effective filing date of the present application. Thus, Applicants submit that Hsieh is not a proper prior art reference under § 102(a).

Hence, Applicants respectfully request withdrawal of this rejection.

2. Claims 39-43, 44-46 and 49 were rejected under 102 (b) as allegedly being anticipated by Brewer *et al.* (WO 98/54963; published 12/10/1998) which discloses a polypeptide approximately 99% identical to polypeptide of SEQ ID NO: 4 of the present application.

Again, as discussed above, the effective filing date of the present application is September 17, 1998. The effective reference date of Brewer is 12/10/1998 which is after the effective filing date of the present application.

Thus, Applicants submit that Brewer is not proper prior art under §102(b) or 102(a) and respectfully request withdrawal of this rejection.

Claim Rejections - 35 USC § 103

Claims 44-46, 49 were rejected under 103 (a) as allegedly being obvious over Hsieh *et al.* (Nature 398: 431-36, 1999) which discloses a polypeptide with 99.7% sequence identity (differs by one amino acid) to SEQ ID NO: 4 of the present application.

Also, Claims 44-46, 49 were rejected under 103(a) as allegedly being obvious over Brewer *et al.* (WO 98/54963; published 12/10/1998) which discloses a polypeptide approximately identical to SEQ ID NO: 4 (differs by 2 amino acids) of the present application.

Since both the references cited above have effective reference dates (1999 for Hsieh and 12/10/1998 for Brewer) after the effective filing date of the present application, namely

September 17, 1998, Applicants submit that neither Hsieh nor Brewer are prior art under § 103(a) and respectfully request withdrawal of this rejection.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C7).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: July 12, 2004

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